CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

https://doi.org/10.5281/zenodo.10002886

https://www.iajps.com/volumes/volume10-september-2023/25-issue-09-september-23/

Available online at: http://www.iajps.com ***Review Article***

REVIEW ON NEW DRUG DEVELOPMENT IN CANCER

Miss. Vasa Kalyani[1], Mr. V. S. Chandrasekaran[2*], Dr. M. Kishore Babu[3]

[1]Final year B Pharmacy, Krishna Teja Pharmacy College, Tirupati – 517 506.

[2]Associate Professor, Department of Pharmaceutical Biotechnology, Krishna Teja Pharmacy College, Tirupati – 517 506.

[3]Professor and Principal, Krishna Teja Pharmacy College, Tirupati – 517 506.

Abstract:

The past decade has seen the publication of a number of new proposals for the design of phase 1 trials of anti-cancer agents. As addressed by the recent Food and Drug Administration Critical Path Initiative, tools are urgently needed to increase the speed, efficiency, and cost-effectiveness of drug development for cancer and other diseases Scientists have revealed details of the discovery of a new cancer drug that could be used to treat a range of cancer types, including some blood cancers andsolid tumors. Recently, the rapid growth of computational tools for drug discovery, including anticancer therapies, has exhibited a significant and outstanding impact on anticancer drug design and has also provided fruitful insights into the area of cancer therapy. Generally, drug developmentis a long process because a potential new drug must be identified and then evaluated in preclinical and clinical studies. The discovery of a potential new drug can occur in several different ways. Researchers may identify a new drug by testing numerous compounds in a laboratory panel to assessfor any beneficial effects, such as stopping cancer cell growth or killing cancer cells.

KEY WORDS: Drug development, Cancer, Clinical Practice, Pharmacogenomics, Cytochrome.

Corresponding author:

Mr. V. S. Chandrasekaran,

Associate Professor,

Department of Pharmaceutical Biotechnology,

Krishna Teja Pharmacy College, Tirupati – 517 506.

QR code

Please cite this article in press V. S. Chandrasekaran et al, ***Review On New Drug Development In Cancer,*** *Indo Am. J. P. Sci, 2023; 10 (09).*

1. INTRODUCTION:

Drug development comprises all the activities involved in transforming a compound from a drug candidate (the end-product of the discovery phase) to a product approved for marketing by the appropriate regulatory authorities. New drugs are required to treat the symptoms of new diseases but also to prevent the spread of new diseases by vaccination. Drug development is the process of bringing a new pharmaceutical drug to the market once a lead compound has been identified through the process of drug discovery [(1)]. Medical research universities, government agencies like the National Cancer Institute (NCI), and pharmaceutical companies find and test new drugs. In drug research, the "sponsor" is the group that develops a drug. They do the initial research needed for the U.S. Food and Drug Administration (FDA) to approve the drug. In the early 1900s, the famousGerman chemist Paul Ehrlich set about developing drugs to treat infectious diseases [(2)]. He was the onewho coined the term "chemotherapy" and defined it as the use of chemicals to treat disease. any ofseveral drugs that control or kill neo-plastic cells; used in chemotherapy to kill cancer cells; all haveunpleasant side effects that may include nausea and vomiting hair loss and suppression of bone marrow function.

Drug development is the process of **BRINGING OF NEW DRUG MOLECULE INTO CLINICAL PRACTICE.**
There are also four stages which are included in new drug development:

A. Early Drug Discovery
B. Pre–Clinical Phase
C. Clinical Phases
D. Regulatory Approval

A. EARLY DRUG DISCOVERY:

The Early Drug Discovery process typically starts by screening for potentially active compounds. These compounds must have a therapeutic effect on the intended disease, and after identifying them, testing for safety and effectiveness begins. The Early Drug Discovery Process involves many different actions and testing. Researchers collaborate to identify and optimize potential leads to a specific target. Essentially, the leads must elicit a desirable effect on a specific biological target implicated in a disease, in the hopes of treating it[(3)].

B. PRE–CLINICAL PHASE:

The discovery phase is followed by a pre-clinical research phase, where the lead compounds are tested both *in vitro* and *in vivo* – experimental models that come as close as possible to resembling humans. Once fully characterized, the most promising compounds become lead candidates. The most important aspect of preclinical research is the rigorous safety tests with the purpose of ensuring that the candidate is not toxic before it can go through clinical studies in humans. Altogether, the discovery phase and the preclinical phase can take four to seven years[(4)]. After completion of the preclinical tests, provided the results positively answer the researchers' hypotheses, developers will apply for permission to proceed with clinical–human studies. This is done either through an *Investigational New Drug (IND)* application in the US or a *Clinical Trial Application* (*CTA*) in the EU. The respective regulator authority then examines all available data and decides whether to approve a move to the clinic.

C. CLINICAL PHASES:

- **Phase 1 safety:**

Following regulatory approval and approval from ethics committees, the first clinical study, a phase I study – which constitutes the first study in humans, is initiated. Here, the candidate is generally tested on 20 to 80 healthy volunteers with the aim of determining whether the candidate behaves in the same way in the human body as the preclinical studies have indicated[(5)].

The safety profile – or toxicity – of the substance is again the main focus, but this time in humans. In phase I you test what constitutes a safe dose, how the drug is absorbed, and how long it is active in the body. It is worth noting that, for safety reasons, phase I clinical trials tend to exclude women of childbearing age.

- **Phase 2 proof-of-concept:**

In the event of positive safety results from Phase I, drug developers can apply for permission to take the next clinical development step – phase II. In this phase, the candidate is most often evaluated in 100 to 300 patients diagnosed with the disease that the candidate is intended to treat. Here, efficacy joins safety as minimum and maximum dosages of the drug are determined for use in the next phase of development. Phase II typically takes up to two years [(5,6)].

D. REGULATORY APPROVAL:

In the event of good results from phases I-III, an application for market approval is submitted, called *New Drug Application* (NDA)*/*Biologics License Application* (BLA) in the US and *Marketing*

Authorization Application (MAA) in the EU. These can include hundreds of thousands of pages of documentation summarizing all collected data from the discovery phase onwards, and where the principal investigator argues for approval with the FDA and/or EMA Preparing the application documentation can take several months, followed by about 6-10 months for the authorities to process the application.

New drug developments are mainly important to treat the symptoms of new diseases but alsoto prevent the spread of new diseases by vaccination. Typically, researchers discover new drugs through new insights into a disease process that allow researchers to design a product to stop or reverse the effects of the disease—many tests of molecular compounds to find possible beneficial effects against any of a large number of diseases. One of the latest advances in cancer treatmentis immunotherapy. It uses the body's immune system to fight against the disease. Immunotherapy can be used to treat several types of cancer. It Is often combined with other treatments, such as surgery or chemotherapy [(7)].

2. CLINICAL TRIAL DESIGNS IN CANCER DRUG DEVELOPMENT:

Phase –l trail design in cancer therapeutics has changed little in 20 years. Unlike most therapeutic areas, there are two goals in cancer trials; precise definition of an optimal (recommended phase-ll).

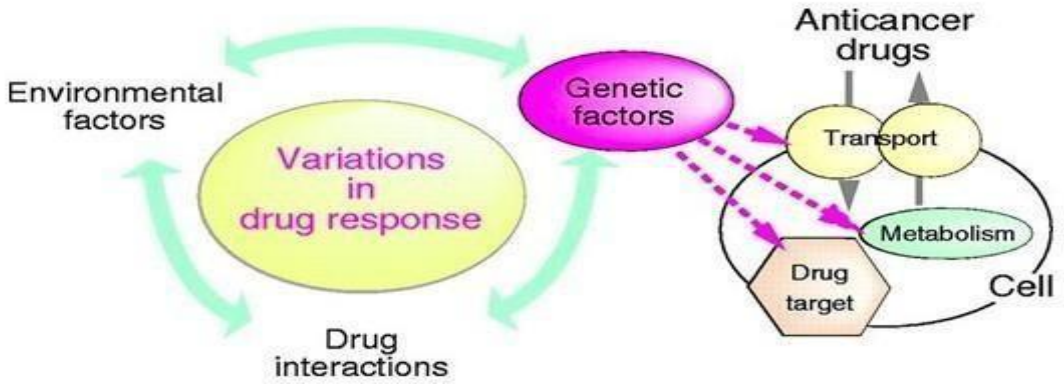
2.1 STARTING DOSE LEVELS FOR CLINICAL TRIAL DESIGN:

As noted above, preclinical studies in mice define a dose at which approximately 10% ofthem ice die (the murine LD10). One-tenth of the murine equivalent LD10 (0.1 MELD10), expressed in milligrams perimeters squared, has Historically been as a starting dose in humans when Toxicologic studies in a second species (eg. rat, dog) do not show substantial differences in the dose –toxicity rlln Ship. Under conditions in which murine toxicity and data from asecond species show no marked inter-species differences (or where the mouse was the most sensitive of the two Species), Eisenhauer asked the question of whether higher Starting doses can be safely used.To address this, our view of compounds evaluated in phase-I trials over the past few years was undertaken [(8)]. Agents selected for review were Cytotoxic drugs studied as single agents in an initial phase I Trial performed to determine the MTD. All published trials of such agents were included, provided their starting dose was based on murine LD10 information. With the knowledge of the "true" MTD determined in each trial, the number of dose-escalation steps to achieve MTD was Calculated based on the actual starting dose of 0.1 MELD1 and theoretical starting doses of 0.2 and MELD10. To Ensure comparability, dose escalation was performed in all Cases according to the modified Fibonacci scheme. The major End points of the exercise were to determine if increasing the starting dose shortened dose escalation and trial length and to assess the safety of the use of higher starting doses [(9)].

3. CANCER PHARMACOGENOMICS: "Powerful Tools In Cancer Chemotherapy And Drug Development."

Pharmacogenomics is a rapidly growing field that aims to elucidate the genetic basis for inter-individual differences in drug response and to use such genetic information to predict the safety, toxicity, and/or efficacy of drugs in individual patients or groups of patients. While drug-drug interactions and environmental factors significantly contribute to inter-individual variability in drug response, genetic factors (e.g., inherited variability of drug targets, drug-metabolizing enzymes, and/or drug transporters) also appear to have a major impact on drug response and disposition. Considering the significant heterogeneity associated with patient responses tochemotherapeutic agents and their narrow therapeutic indices, pharmacogenomics has the potential to offer individualized cancer treatment regimens [(10)]. Clearly, a better understanding of the genetic determinants of chemotherapeutic response will enable the prospectiveidentification of patients at risk for severe toxicity or those most likely to benefit from a particular treatment regimen. Such studies can be translated to clinical practice via molecular diagnostics (genotyping) in order to guide the selection of the optimal drug combination and dosage for the individual patient. A number of detailed reviews on cancer pharmacogenomics have been published recently. This article focuses on the current and future applications of pharmacogenomics in clinical cancer therapy and cancer drug development (figure 1).

Figure 1



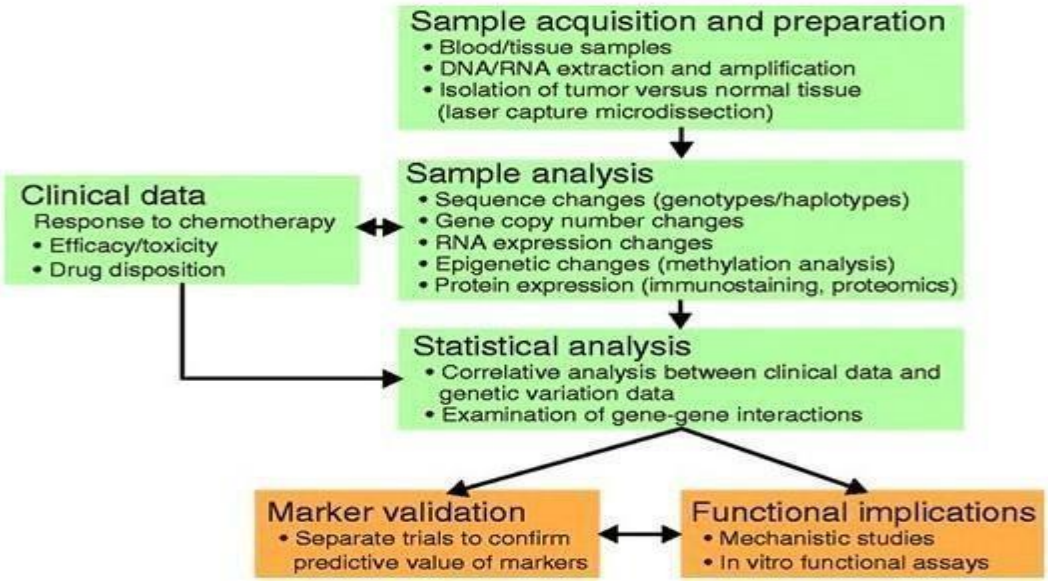
4. GENETIC VARIATIONS AFFECTING DRUG RESPONSE AND TOXICITY WITH CANCER CHEMOTHERAPY:

Pharmacogenomic approaches have been applied to many existing chemotherapy agents in an effort to identify relevant inherited variations that may better predict patient response to chemotherapy.

Genetic variations include nucleotide repeats, insertions, deletions, and single nucleotide polymorphisms (SNPs), which can alter the amino acid sequence of the encoded proteins, RNA splicing, and gene transcription. Such genetic polymorphisms in drug-metabolizing enzymes, transporters, and molecular targets have been actively explored with regard to functional changes in phenotype (altered expression levels and /or activity of the encoded proteins) and their contribution to variable drug response [(11)]. Recent studies also indicate that genetic variations vary substantially among different ethnic groups and that the evaluation of the haplotypes (a combination of polymorphisms that are inherited together) can often result in a better correlation with phenotypes than with individual polymorphisms. The following sections describe some clinically relevant examples of genetic polymorphisms to illustrate the relevance of cancer pharmacogenomics in optimizing chemotherapy as a way to enhance efficacy and safety (figure 2).

PHARMACOGENOMICS TO DRUG DEVELOPMENT:

Figure 2

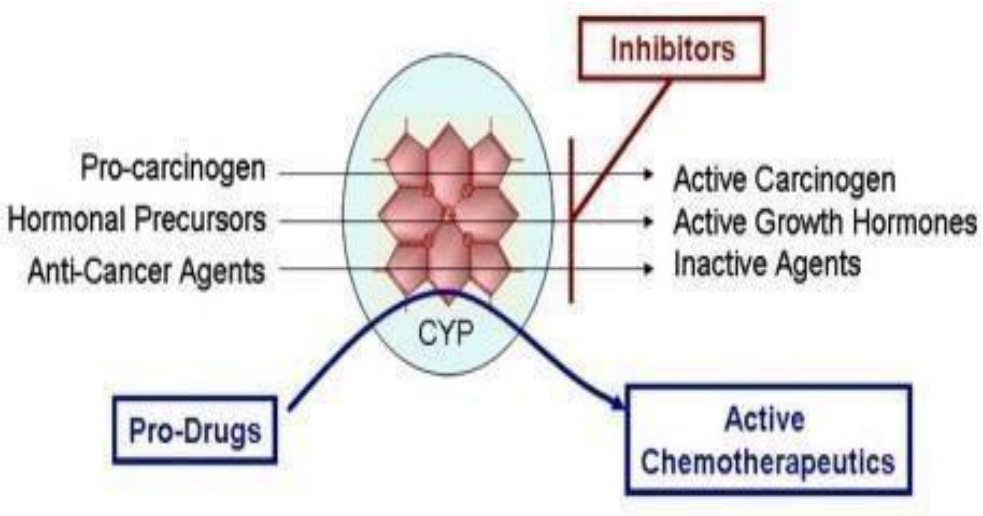


4.1 Targeting cytochrome P450 enzymes: A new approach in anti-cancer drug development

Cytochrome P450s (CYPs) represent a large class of heme-containing enzymes that catalyze the metabolism of multitudes of substrates both endogenous and exogenous. Until recently, however, CYPs have been largely overlooked in cancer drug development, acknowledgedonly for their role in phase I metabolism of chemotherapeutics. The first successful strategy targeting CYP enzymes in cancer therapy was the development of potent inhibitors of CYP19 (aromatase) for the treatment of breast cancer. Aromatase inhibitors ushered in a new era in hormone ablation therapy for estrogen-dependent cancers, and have paved the way for similar strategies (i.e., inhibitionof CYP17) that combat androgen-dependent prostate cancer. Identification of CYPs involved in the inactivation of anti-cancer metabolites of vitamin D3 and vitamin A has triggered the development of agents that target these enzymes as well. The discovery of the over-expression of exogenous metabolizing CYPs, such as CYP1B1, in cancer cells has roused interest in the development of inhibitors for chemoprevention and of prodrugs designed to be activated by CYPs only in cancer cells[12,13]. Finally, the expression of CYPs within tumors has been utilized in the development of bio-reductive molecules that are activated by CYPs only under hypoxic conditions (figure 3).

Graphical picture of targeting cytochrome ep450:

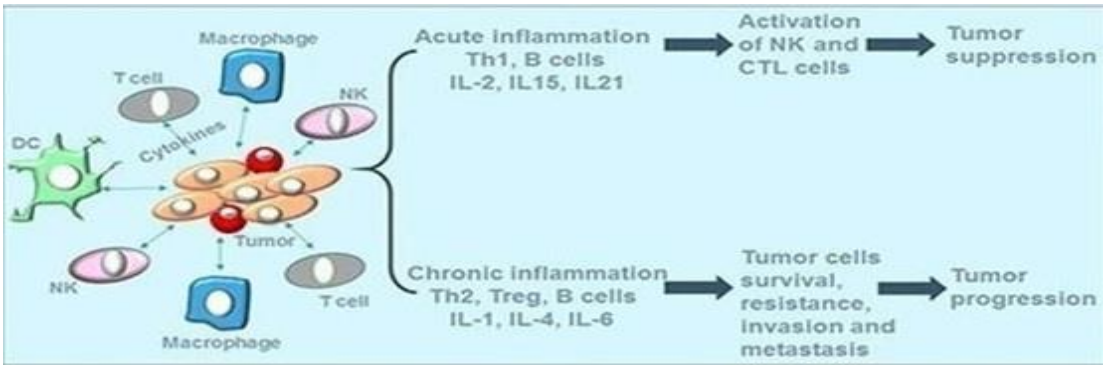
Figure 3:



5. Tumor-related interleukins: old validated targets for new anti-cancer drug development

The tumor microenvironment is rich in a variety of immune cells, composed of both myeloid (innate immunity) and lymphoid (adaptive immunity) lineages. The former involves macrophages, granulocytes, mast cells, dendritic cells (DCs), and natural killer (NK) cells. Contrary to what was thought,not all these leukocytes represent an attempt by the host to eradicate transformed neoplastic cells. Only some are, and all other classes may support tumor growth, invasion, metastasis, and escape from the host immune response and conventional anti-cancer therapy [14,15]. On the other hand, adaptive immunity Is generally represented by Band T lymphocytes. Acute activation of B cells may play a role in eradicating early neoplastic cells, or inducing tumor regression via the secretion of antigen-specific immune globulins; meanwhile, the chronic activation of B cells may paradoxically play a role inpotentiating cancer development. Moreover, cytotoxic T lymphocytes (CTLs) recruit Edina cute tumor-directed immune responses, and appear to protect against tumor development, whereas the immune responses involving chronic activation of humoral immunity and infiltration of the cells result in the promotion oftumor development and disease progression. the regulation of such immune responses is mediated by the cytokines secreted to initiate or weaken the host anti-tumor immunity (figure 4).

Figure 4:



5.1 Progress in chemoprevention drug development:

In most epithelial tissues, accumulating mutations (i.e., genetic progression) and loss of cellular control functions cause progressive phenotypic changes from normal histology to early pre-cancer [intraepithelial neoplasia (IEN)] to increasingly severe IEN to superficial cancer and finally to invasive disease. This process can be relatively aggressive in some settings (e.g., in the presence of a DNA repair–deficient genotype) but generally occurs relatively slowly over years and decades. Cancer chemoprevention can be defined as the prevention of cancer or treatment of identifiable pre-cancers (defined as histopathologic or molecular IEN). The long latency to invasive cancer is a major scientific opportunity but also an economic obstacle to showing the clinical benefit of candidate chemo-preventive drugs.

Therefore, an important component of chemo-preventive agent development research in recent years has been to identify earlier (than cancer) endpoints or biomarkers that accurately predict an agent's clinical benefit or cancer incidence–reducing effect. In many cancers, IEN is an early endpoint

5.2 Molecular Biomarkers in Chemoprevention:

There are opportunities for using molecular biomarkers in all aspects of chemoprevention. For example, these biomarkers may be molecular targets used for identifying new agents or optimizing lead agents. They can be cancer risk markers for selecting cohorts for chemo-preventive studies, and their presence may predict response to mechanism-based interventions. In addition, modulation of these biomarkers in animal and early clinical studies is useful in determining the delivery of biologically effective doses. Because many chemo-preventive agents are likely to be used chronically by essentially healthy people, assuring safety on long-term drug treatment is critical. Molecular biomarkers of potential toxicity, such as patterns of activity of drug-metabolizing enzymes, could become very useful in evaluating candidate agents in preclinical development and in monitoring subjects in clinical trials (Table 1).

TABLE 1. CHARACTERISTICS OF NEOPLASIA AND ASSOCIATED MOLECULAR BIOMARKERS

CHARACTERISTICS OF NEOPLASIA	POSSIBLE MOLECULAR TARGETS
Self-sufficiency in cell growth	Epidermal growth factor, platelet-derived growth factor, MAPK, PI13k
Insensitivity to anti-growth signals	SMADs, pRb, cyclin-dependent kinases, MYC.
Limitless replicative potential	hTERT,pRb,p53
Evading apoptosis	BCL- 2,BAX,capases,FAS,tumornecrosisfactorrecepto r,DR5,IGF/PTEN,ras,interleukin-3,NF-kB
Sustained angiogenesis	VEGF, basic fibroblast growth factor,thrombospondin-1,hypoxia-inducible factor -1
Tissue invasion and metastasis	Matrix metal proteinases, MAPK, E-cadherin

6. Limitations and Challenges Associated with Traditional Anticancer Therapies:

- **Surgery:**

1. The limitation of surgery lies in how deep-seated a tumor tissue is as well as its size.
2. If the tumor size is perilously big, it can seriously impair the regular functioning of a Surrounding tissue or organ.
3. A relevant example, post brain surgery, is a negative impact on the normal functioning of the brain., like thinking, speaking, etc. In this situation, surgery may not be a first preference for treatment.
4. Another pertinent example is breast cancer where accurate determination of tumors and position remains a challenge and, therefore, limits the success of a surgical procedure

- **Chemotherapy:**

1. Chemotherapy is a treatment regime where a combination of drugs is administered to the body. Notably, chemotherapy remains one of only a few treatment choices for advanced-stage cancer (metastasized cancer);
2. However, a serious deficiency of chemotherapy is the lack of its target selectivity.
3. As the cancer cells arise from normal functioning cells that exhibit uncontrolled growth, anticancer drugs in discriminately impact the growth of normal non-proliferative cells along with inhibiting cancer cell growth.
4. This poor selectivity of common chemotherapeutic drugs imparts serious side effects on normal tissues such as bone marrow, hair follicles, and the gastrointestinal tract.

- **Radiotherapy:**

1. Radiotherapy is another prominent anticancer therapy and is characterized by the use of high-energy radiation for the treatment of cancer.
2. The wide application of radiotherapy varies from eliminating tumors to reducing tumor size.
3. One way in which radiotherapy differs from chemotherapy is that the adverse effects of radiotherapy are localized in nature (in proximity to the radiated area) as opposed to systemic adverse effects manifested by chemotherapy. The side effects of radiation therapy can beclassified either as early or late effects.
4. While early effects are reversible the late effects have a propensity to be irreversible and aggravate with time, and the more involved To Have a propensity to be irreversible and aggravate with time. The more involved late effects are facilitated by stromal, parenchymal, inflammatory, and endothelial cells.

7. CONCLUSION:

A plan for the diagnosis and treatment of cancer is a key component of any overall cancer control plan. Its main goal is to cure cancer patients or prolong their life considerably, ensuring a good quality of life. In order for a diagnosis and treatment program to be effective, it must never be developed in isolation. It needs to be linked to an early detection program so that cases are detected at an early stage when treatment is more effective and there is a greater chance of cure. It also needs to be integrated with a palliative care program, so that patients with advanced cancers, who can no longer benefit from treatment, will get adequate relief from their physical, psychosocial, and spiritual suffering.

Furthermore, programs should include an awareness-raising component, to educate patients, family, and community members about the cancer risk factors and the need for taking preventive measures to avoid developing cancer. Where resources are limited, diagnosis and treatment services should initially target all patients presenting with curable cancers, such as breast, cervical, and oral cancers that can be detected early.

8. REFERENCE:

1. Dent S F, Eisenhauer EA: Phase I trial design: A renewed methodologies being put into practice. S F Dent *et al* oncology.1996.
2. Goodman S N, Zahurak ML, Piantadosi S: Some practical improvements in the continual re-assessment method for phase I studies. Stat Med14:1149-1161,1995.
3. Kerr D J, Walkman P, editors. New molecular targets for cancer chemotherapy. BocaRaton (FL): C R C Press;1994.
4. Nyfors A. Methotrexate therapy of psoriasis: an effect and side-effects with particular reference to hepatic changes. A survey. *Dan MedBull*1980; 27:74–96.
5. World Health Organization. WHO handbook of reporting results of cancer treatment. Geneva: World Health Organization,1979.
6. Mckeown S R. Defining normoxia, hypoxia and hypoxia in tumours-implication for treatment response. 2014; 87: 20130676. [PubMed],[WebofScience®],[GoogleScholar]
7. Adams GE, Dewey DL. Hydrated electrons and radiobiological sensitization. Biochemistry Biophysics Research Community.1963; 12:473–7 [Crossref],[PubMed], [WebofScience ®], google

scholar.
8. Tiana M, Villar D, Perez-Guijarro E, *et al*. A role for insulator elements in the regulation of gene expression response to hypoxia. Nucleic Acids Res2012;40:1916– 27[Crossref], [PubMed], [WebofScience ®], [GoogleScholar]
9. Atkins C, Liu Q, Minthorn E, *et al*. Characterization of a novel PERK kinase inhibitor with anti-tumor and anti-angiogenic activity. Cancer Research 2013;73:1993– 2002 [Crossref], [PubMed], [WebofScience ®],[GoogleScholar]
10. Weissmann N, Zeller S, Schafer R U,*et al*. Impact of mitochondria and NADPHoxidases on acute and sustained hypoxic pulmonary vasoconstriction. American Journal Respiratory Cell Molecular Biology. 2006;34:505
11. Casey JR, Grinstein S, Orlowski J. Sensors and regulators of intracellular pH. Nat Rev Mol CellBiol2010;11:50–61 [Crossref],[PubMed], [WebofScience ®], [Google Scholar]
12. Doss M, Zhang JJ, Belanger MJ, et al. Biodistribution and radiation dosimetry of the hypoxia marker 18F- HX4 in monkeys and humans were determined by using whole-body PET/CT. Nuclear Medical Community. 2010;31:1016–24[Crossref], [PubMed], [WebofScience ®], [Google Scholar].
13. Supuran C T . Carbonican hydrases: from biomedical applications of the inhibitors and activators to biotechnological use for CO(2) capture. J Enzyme Inhibition Medical Chemistry. 2013;28;229–32 [Taylor & Francis [Online], [Web ofScience®],[GoogleScholar]
14. Balk will F, Mantovani A. Inflammation and cancer: back to Virchow. Lancet. 2001; 357:539–45.
15. Yamamoto Y, Gaynor R B. Therapeutic potential of inhibition of the NF-κB pathway in the treatment of inflammation and cancer. Journal of Clincal in vest. 2001;107: 135–142.